SCIENTIFIC ABSTRACT OF THE PROTOCOL

The proposed study is designed to test the safety and efficiency of gene transfer to the lung and nose of cystic fibrosis patients (CF) utilizing a cationic lipid:pDNA complex (67A:pCF1-CFTR) encoding the cDNA for the cystic fibrosis transmembrane conductance regulator (CFTR). The delivery vehicle consists of a proprietary aerosol formulation of 67:DOPE. The cationic lipid:pDNA aerosol formulation has been optimized for the transfection of CF epithelial cells *in vitro* and lung epithelial cells *in vivo*. The 67A:pCF1-CFTR complex is formed by mixing the delivery vehicle (67A) with pDNA (pCF1-CFTR) at the appropriate ratio and concentration. The pCF1-CFTR component has been developed to maximize expression of the CFTR cDNA in CF epithelial cells.

The proposed clinical trial is a single dose trial designed to test the safety of the cationic lipid:plasmid formulation 67A:pCF1-CFTR in the lungs and nose of CF patients. In order to minimize the risk to CF patients, the dose to be used for aerosol delivery to the lungs of CF patients was determined by testing the lipid formulation (67A) alone in the lungs of normal volunteers in Genzyme clinical trial CF95L-1101: *Safety of aerosol administration of escalating doses of a cationic lipid formulation to the lungs of normal volunteers*. The highest tested dose (114.4 mg 67A) was determined to be safe by the absence of systemic toxicity and absence of a clinically significant change in lung function. The cationic lipid formulation 67A will be complexed with pCF1-CFTR DNA at a 6:8 molar ratio (total lipid @ 14.3 mg/mL:pCF1-CFTR @ 2.64 mg/mL) for aerosol administration of 16 mL to each CF patient in this trial.

Safety of the 67A:pCF1-CFTR complex will be assessed by physical exams, measurements of inflammatory mediators, by routine blood and urine analyses and assessment of CT scans and pulmonary function. Efficacy will be assessed by comparing Vt measurements taken prior to treatment and for several days post-treatment. Gene transfer will be assessed by RT-PCR analysis of cells obtained post-treatment by brush samples and biopsy.

Information derived from this protocol will add to our knowledge of the safety and efficiency of cationic lipid:pDNA complexes and will guide the design of subsequent protocols utilizing cationic lipid vectors targeted to the respiratory airways of CF patients.